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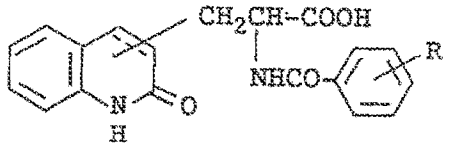
(54) Title: AGENT FOR INCREASING SOMATOSTATIN OR FOR INHIBITING DECREASE OF SOMATOSTATIN



(I)

(57) Abstract

An agent for increasing secretion of somatostatin or inhibiting decrease of secretion of somatostatin which comprises as an active ingredient a carbostyril compound of formula (I), or a salt thereof, which is useful for treating diseases associated with the decrease of somatostatin such as esophagitis, Alzheimer's disease, etc.

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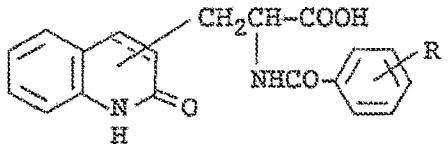
DESCRIPTION

Agent for Increasing Somatostatin or for Inhibiting Decrease of Somatostatin

Technical Field

This invention relates to an agent for increasing secretion of somatostatin or for inhibiting decrease of secretion of somatostatin in the bio-body. More particularly, it relates to a pharmaceutical composition useful for increasing secretion of somatostatin or for inhibiting decrease of section of somatostatin which comprises as an esstial active ingredient a carbostyril compound of the formula:



(I)

wherein R is a halogen atom, and the propionic acid substituent is substituted at 3- or 4-position on the carbostyril nucleus, and the bond between 3- and 4-positions is single or double bond, or a pharmaceutically acceptable salt thereof, preferably 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or a pharmaceutically acceptable salt thereof.

Prior Art

It is known that somatostatin is a growth hormone-release inhibiting factor secreted in the bio-body and when the secretion of somatostatin is decreased, there are induced various diseases, such as esophagitis, Zollinger-Ellison syndrome, diarrhea, erethistic colitis, various cancers, hepatitis, portal hypertension, headache, migraine, Alzheimer's

disease, presbyophrenia, pancreatitis, acromegalia.

The present inventors have intensively studied to find a new drug useful for treating the diseases associated with the decrease of somatostatin, and have found that the carbostyril compounds of the above formula (I), particularly 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or a pharmaceutically acceptable salt thereof, are useful as an agent for increasing secretion of somatostatin or for inhibiting decrease of secretion of somatostatin.

The carbostyril compounds of the formula (I) and processes for the preparation thereof are disclosed in Japanese Patent Second Publication (Kokoku) No. 35623/1988, wherein it is disclosed that the carbostyril compounds are useful as an anti-ulcer drug.

Summary of the Invention

This invention provides an agent for increasing secretion of somatostatin or inhibiting decrease of secretion of somatostatin comprising as an essential active ingredient a carbostyril compound of the formula (I) or a pharmaceutically acceptable salt thereof, a method of the treatment of diseases associated with decrease of somatostatin by administering the agent as set forth above, and use of the agent for the treatment of diseases associated with decrease of somatostatin.

Detailed Description of the Invention

The agent of this invention is usually in the form of conventional pharmaceutical preparations, for example, preparations suitable for oral administration such as tablets, pills, powders, granules, capsules, solutions, suspensions,

emulsions, and preparations for parenteral administration such as suppositories and injections (e.g. solutions, suspensions, etc.). These preparations can be prepared by a conventional method with conventional pharmaceutically acceptable carriers or diluents, such as fillers, thickening agents, binders, wetting agents, disintegrators, surfactants, lubricants, and the like.

In order to form in tablets, there are used conventional pharmaceutically acceptable carriers such as vehicles (e.g. lactose, white sugar, sodium chloride, glucose, urea, starches, calcium carbonate, kaolin, crystalline cellulose, silicic acid, etc.), binders (e.g. water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethyl cellulose, shellac, methyl cellulose, potassium phosphate, polyvinylpyrrolidone, etc.), disintegrators (e.g. dry starch, sodium arginate, agar powder, laminaran powder, sodium hydrogen carbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium laurylsulfate, stearic monoglyceride, starches, lactose, etc.), disintegration inhibitors (e.g. white sugar, stearin, cacao butter, hydrogenated oils, etc.), absorption promoters (e.g. quaternary ammonium base, sodium laurylsulfate, etc.), wetting agents (e.g. glycerin, starches, etc.), adsorbents (starches, lactose, kaolin, bentonite, collidal silicates, etc.), lubricants (e.g. purified talc, stearates, boric acid powder, polyethylene glycol, etc.), and the like. Moreover, the tablets may also be in the form of a conventional coated tablet, such as sugar-coated tablets, gelatin-coated tablets,

enteric coated tablets, film coating tablets, or double or multiple layer tablets.

In the preparation of pills, the carriers include vehicles (e.g. glucose, lactose, starches, cacao butter, hydrogenated vegetable oils, kaolin, talc, etc.), binders (e.g. gum arabic powder, tragacanth powder, gelatin, ethanol, etc.), disintegrators (e.g. laminaran, agar, etc.), and the like.

In the preparation of suppositories, the carriers include, for example, polyethylene glycol, cacao butter, higher alcohols, higher alcohol esters, gelatin, semi-synthetic glycerides, and the like.

Capsules can be prepared by charging a mixture of the compound of this invention with the above carriers into hard gelatin capsules or soft capsules in a usual manner.

In the preparation of injections, the solutions, emulsions or suspensions are sterilized and are preferably made isotonic with the blood. In the preparation of these solutions, emulsions and suspensions, there are used conventional diluents, such as water, ethyl alcohol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, polyoxyethylene sorbitan fatty acid esters, and the like. In this case, the pharmaceutical preparations may also be incorporated with sodium chloride, glucose, or glycerin in an amount sufficient to make them isotonic, and may also be incorporated with conventional solubilizers, buffers, anesthetizing agents. Besides, the pharmaceutical preparations may optionally be incorporated with coloring agents, preservatives, perfumes, flavors, sweeting agents, and other medicaments, if required.

The agent for increasing secretion of somatostatin or inhibiting decrease of secretion of somatostatin of this invention is useful for the treatment of diseases associated with the decrease of somatostatin, such as esophagitis, Zollinger-Ellison syndrome, diarrhea, erethistic colitis, various cancers, hepatitis, portal hypertension, headache, migraine, Alzheimer's disease, presbyophrenia, pancreatitis, acromegalia.

The amount of the active component carbostyril compound of this invention to be incorporated into the preparations is not specified but may be selected from a broad range, but it is usually in the range of from 1 to 70 % by weight, preferably in the range of 5 to 50 % by weight.

The somatostatin-increasing or decrease-inhibiting agent of this invention may be administered in any method, and suitable method for administration may be determined in accordance with various forms of preparation, ages, sexes and other conditions of the patients, the degree of severity of diseases, and the like. For instance, tablets, pills, solutions, suspensions, emulsions, granules and capsules are administered orally. The injections are intraveneously administered alone or together with a conventinal auxiliary liquid (e.g. glucose, amino acid solutions), and further are optionally administered alone in intramuscular, intracutaneous, subcutaneous, or intraperitoneal route, if required. suppositories are administered in intrarectal route.

The dosage of the agent of this invention may be selected in accordance with the usage, ages, sexes and other

conditions of the patients, the degree of severity of the diseases, and the like, but is usually in the range of about 0.6 to 50 mg of the active compound of this invention per 1 kg of body weight of the patient per day. The active compound is preferably contained in the pharmaceutical preparations in an amount of 10 to 1000 mg per the dosage unit.

Examples

The somatostatin-increasing or decrease-inhibiting agent of this invention is illustrated by the following Preparations and Pharmacological experiments.

Preparation 1

Film coated tablets are prepared from the following components.

Components	Amount
2-(4-Chlorobenzoylamino)-3-(2-quinolon-4-yl)-propionic acid	150 g
Abicel (tradename of microcrystalline cellulose, manufactured by Asahi Chemical Industry Co., Ltd., Japan)	40 g
Corn starch	30 g
Magnesium stearate	2 g
Hydroxypropyl methylcellulose	10 g
Polyethylene glycol-6000	3 g
Castor oil	40 g
Ethanol	40 g

The active component of this invention, Avicel, corn starch and magnesium stearate are mixed and kneaded and the mixture is tabletted using a conventional pounder (R 10 mm) for sugar coating. The tablets thus obtained are coated with a film coating agent consisting of hydroxypropyl methylcellulose, poly-

ethylene glycol-6000, castor oil and ethanol to give film coated tablets.

Preparation 2

Tablets are prepared from the following components.

Components	Amount
2-(4-Chlorobenzoylamino)-3-(2-quinolon-4-yl)-propionic acid	150 g
Citric acid	1.0 g
Lactose	33.5 g
Dicalcium phosphate	70.0 g
Pluronic F-68	30.0 g
Sodium laurylsulfate	15.0 g
Polyvinylpyrrolidone	15.0 g
Polyethylene glycol (Carbowax 1500)	4.5 g
Polyethylene glycol (Carbowax 6000)	45.0 g
Corn starch	30.0 g
Dry sodium laurylsulfate	3.0 g
Dry magnesium stearate	3.0 g
Ethanol	q.s.

The active compound of this invention, citric acid, lactose, dicalcium phosphate, Pluronic F-68 and sodium laurylsulfate are mixed. The mixture is screened with No. 60 screen and is granulated in wet with an alcohol solution containing polyvinylpyrrolidone, carbowax 1500 and 6000. If required, an alcohol is added thereto so that the powder mixture is made a paste-like mass. Corn starch is added to the mixture and the mixture is continuously mixed to form uniform particles. The resulting particles are passed through No. 10 screen and entered into a tray and then dried in an oven at 100°C for 12

to 14 hours. The dried particles are screened with No. 16 screen and thereto are added dry sodium laurylsulfate and dry magnesium stearate, and the mixtue is tabletted to form the desired shape.

The core tablets thus prepared are vanished and dusted with talc in order to guard from wetting. Undercoating is applied to the core tablets. In order to administer the tablets orally, the core tablets are vanished several times. In order to give round shape and smooth surface to the tablets, further undercoating and coating with lubricant are applied thereto. The tablets are further coated with a coloring coating material until the desired colored tablets are obtained. After drying, the coated tablets are polished to obtain the desired tablets having uniform gloss.

Preparation 3

An injection preparation is prepared from the following components.

Components	Amount
2-(4-Chlorobenzoylamino)-3-(2-quinolon-4-yl)-propionic acid	5 g
Polyethylene glycol (molecular weight: 4000)	0.3 g
Sodium chloride	0.9 g
Polyoxyethylene sorbitan monooleate	0.4 g
Sodium metabisulfite	0.1 g
Methyl-paraben	0.18 g
Propyl-paraben	0.02 g
Distilled water for injection	10.0 ml

The above parabens, sodium metabisulfite and sodium chloride are dissolved in distilled water of half volume of the

above with stirring at 80°C. The solution thus obtained is cooled to 40°C, and the active compound of this invention and further polyethylene glycol and polyoxyethylene sorbitan monooleate are dissolved in the above solution. To the solution is added distilled water for injection to adjust to the desired volume, and the solution is sterilized by filtering with an appropriate filter paper to give an injection preparation.

Pharmacological Test 1

Male Wistar rats were freely haven take 5 mM sodium taurocholate with drinking water. After 6 months, the administration of sodium taurocholate was stopped and then the active compound of this invention 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid (hereinafter referred to "Compound A") was orally administered in doses of 6 mg/kg/day or 60 mg/kg/day together with a feed. After Compound A was administered for 4 weeks, the rats were killed and the stomach was removed. The mucosal membrane of stomach was collected by scraping, and the content of somatostatin in the gastric mucosa was measured by radioimmunoassay. In the reference group, the above was repeated except that Compound A was not administered and the content of somatostatin in the gastric mucosa was measured likewise, and further in the normal control group to which no sodium taurocholate was administered, the content of somatostatin was measured likewise.

The results are shown in the following Table 1.

Table 1

Treated groups	Dose (mg/kg/day)	Content of somatostatin (ng/g)
Normal group	-	45.4
Reference group	-	19.1
Compound A-administered group	6	28.1
	60	40.7

As is clear from the above results, Compound A of this invention inhibited dose-dependently the decrease of somatostalin content.

Pharmacological Test 2

Normal rats were fed with a solid feed mixed with Compound A for four weeks, whereby Compound A was administered in an amount of 6 mg/kg/day, 60 mg/kg/day or 100 mg/kg/day. After Compound A was administered, the mucosal membrane of stomach was collected like in the above test 1. The brain was also removed. The content of somatostatin in the gastric mucosa and in the brain was measured likewise. In the control group to which no Compound A was administered, the content of somatostatin was measured likewise.

The results are shown in the following Table 2.

Table 2

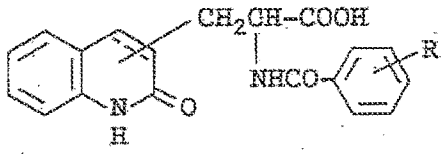
Treated groups	Dose (mg/kg /day)	Content of somatostatin in gastric mucosa (ng/g of tissue weight in wet)	Content of somatostatin in the brain (ng/g of tissue weight in wet)
Control group	-	274 ± 60 (9)*	54 ± 4 (9)*
Compound A-administered group	6	471 ± 79 (10)	101 ± 13 (10)
	60	595 ± 88 (10)	98 ± 13 (10)
	100	714 ± 81 (10)	128 ± 11 (9)

*) The number within the parenthesis means number of animals.

It is clear from the above results that the administration of Compound A of this invention in an amount of 6, 60 and 100 mg/kg/weight increased the content of somatostatin in the gastric mucosa in the ratio of 72, 117, 161 % respectively in comparison with the content in the control group: 274 ± 60 ng/g of tissue weight in wet, and also increased the content in the brain in the ratio of 87, 81 and 137 % respectively in comparison with the content in the control group: 54 ± 4 ng/g of tissue weight in wet.

CLAIMS

1. An agent for increasing secretion of somatostatin or for inhibiting decrease of secretion of somatostatin, which comprises as an essential active ingredient a carbostyril compound of the formula:



(I)

wherein R is a halogen atom, and the propionic acid substituent is substituted at 3- or 4-position on the carbostyril nucleus, and the bond between 3- and 4-positions is single or double bond, or a pharmaceutically acceptable salt thereof.

2. The agent according to claim 1, wherein the active ingredient is 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)-propionic acid or a pharmaceutically acceptable salt thereof.

3. A method for increasing secretion of somatostatin or inhibiting decrease of secretion of somatostatin, which comprises administering an effective amount of the carbostyril compound as set forth in claim 1 or a pharmaceutically acceptable salt thereof to a subject.

4. The method according to claim 3, wherein the active carbostyril compound is 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP 93/00545

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K31/44

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	FOLIA PHARMACOL. JPN. vol. 97, no. 6, 1991, pages 371 - 380 S.KAWANO ET AL. 'PROTECTIVE EFFECT OF REBAMIPIDE (OPC-12759) ON THE GASTRIC MUCOSA IN RATS AND HUMANS' see page 377; table 3	1-4
A	'DORLAND'S ILLUSTRATED MEDICAL DICTIONARY, 26TH EDITION' 1985 , W.B.SAUNDERS COMPANY , PHILADELPHIA see page 1222	1-4
A	DE,A,3 324 034 (OTSUKA PHARMACEUTICAL CO. LTD.) 5 January 1984 see page 24 - page 25	1-4

[10] Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
16 JULY 1993	03.08.93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	THEUNS H.G.

Form PCT/ISA/210 (second sheet) (January 1985)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 93/00545

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: Although claims 3-4 are directed to a method of treatment of the human body the search was based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. JP 9300545
SA 73157

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A-3324034	05-01-84	JP-C- 1490120	07-04-89
		JP-A- 59007168	14-01-84
		JP-B- 63035623	15-07-88
		JP-C- 1665247	19-05-92
		JP-B- 3028425	19-04-91
		JP-A- 59007169	14-01-84
		AT-B- 385506	11-04-88
		AU-B- 552717	19-06-86
		AU-A- 1653683	12-01-84
		BE-A- 897208	04-01-84
		CA-A- 1247624	27-12-88
		CH-A- 654578	28-02-86
		FR-A,B 2530626	27-01-84
		GB-A,B 2123825	08-02-84
		NL-A- 8302390	01-02-84
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		SE-A- 8303813	06-01-84
		US-A- 4578381	25-03-86